REMARKS

Claims 1, 19, 23, 26 and 31-40 are pending. Applicants have previously canceled claims 2-18, 20-21, 24-25 and 27-30. Applicants again reserve the right to present any canceled or withdrawn subject matter in one or more continuation or divisional applications.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1, 19, 23, 26, 31 and 35 under 35 U.S.C. § 112, first paragraph because the specification is allegedly not enabled for the use of a monoester or diester of probucol to enhance the cytotoxicity of any antineoplastic drug for treatment of any disorder of abnormal cell proliferation.

The Examiner asserts that the breadth of the claims is not enabled in part because of the unpredictability of *in vivo* delivery and determination of proper dosage, which require empirical data. According to the Examiner, the unpredictability of *in vivo* cancer therapy supports a rejection under §112. Applicants point out that the requirement that ideal dosing and formulation for human therapy be empirically tested is a feature of all pharmaceutical patents and enablement of a method of use of a pharmaceutical agent cannot rest on the perfection of therapy in humans. The specification provides extensive teaching as to how to prepare a pharmaceutical formulation (see pages 49-53). Furthermore, based on the Examples, a skilled practitioner has guidance to test any particular combinations or dosages for C/EBPβ phosphorylation to ensure that the formulation is effective in the method. Anyone of skill in the art would know that the exact combinations and dosage forms are subject to testing, however based on the direction provided in the specification and the level of skill in the art (which the

Examiner acknowledges is high), the specification provides sufficient enablement for the use of a mono- or di-ester of probucol for enhancing the cytotoxicity of an antineoplastic agent.

The Examiner also asserts that, although use of various antioxidants for countering chemotherapy-induced toxicity was known, it was 'much less certain' whether antioxidants 'in general' enhance antineoplastic cytotoxicity. Applicants bring the Examiner's attention to the limitations of the pending claims, which recite an antioxidant "wherein the antioxidant is a mono or diester of probucol." Therefore the Examiner's assertion that the claimed subject matter is unduly broad appears erroneous.

The Examiner also apparently relies on one possible mechanism of colorectal cancer (used in the Examples) to assert that this cancer is 'unlike other cancers' in being characterized by an accumulation of mutations in the p53 tumor suppressor gene and the Examples thus do not provide full enablement for the claimed method. In this regard, please note that mutations in p53 have been identified in many other cancers, including ovarian, breast, urinary, head and neck, lung, and glioma, among others (for examples see Entrez Gene from NCBI, National Library of Medicine; also PubMed). A search of the literature reveals over *10,000* articles published on the association of p53 mutations with cancers. Colorectal cancer is certainly not unique in this regard.

On at least pages 8-10, 21-23 of the specification, Applicants provided a description of a mechanism of action of the claimed antioxidants and state that the elucidation of this mechanism represents a "fundamental" discovery that provides the basis for the claimed uses. The described mechanism includes the phosphorylation of C/EBPβ and subsequent nuclear localization. The Examples provide support that antioxidants acting through this mechanism enhance cytotoxicity of antineoplastic drugs. Based on the extensive description of the mechanism of action and the

27 examples of methods to test these compounds, anyone of skill in the art is provided a method of evaluating the utility of any particular formulations of compounds.

Rejection under 35 U.S.C. § 103

Claims 1, 19, 26 and 35 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious in view of Siveski-Iliskovic, *et al.*, *Circulation*, Vol. 91 (1), pp. 10-15 (1995) and Parthasarathy (U.S. Patent No. 5,262,439). According to the Examiner, Siveski-Iliskovic teaches the co-administration of probucol with adriamycin, an antineoplastic drug, in a mammal (rat) in order to treat the solid growth of abnormally proliferating cells and to protect against the toxic side effects of adriamycin. Parthasarathy teaches the use of water soluble probucol derivatives that are hydrolyzed to the parent probucol molecule *in vivo*.

For a claim to be obvious, there must be a) a suggestion or motivation to combine reference teachings, b) a reasonable expectation of success, and c) the references must teach all of the claim limitations, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

a) There is no motivation to combine the teaching of Siveski-Iliskovic with Parthasarathy for the claimed method of increasing the cytotoxicity of an antineoplastic agent.

Siveski-Iliskovic describes the effects of probucol when it is co-administered with adriamycin in order to examine whether probucol affords protection against adriamycin-induced cardiomyopathy, and to determine whether probucol has an effect on the antitumor properties of adriamycin. There is *no* mention or suggestion of the use of mono- or di-esters of probucol for enhancing the cytotoxicity of an antineoplastic drug. Although the reference suggests that the parent molecule of probucol may reduce certain toxic side effects, the reference *teaches away* from the possibility that probucol or any of its derivatives would be useful in enhancing

cytotoxicity of antineoplastic agents, as the data provided in rat models showed that co-administration of probucol and adriamycin *did not* significantly reduce tumor size when compared to the administration of adriamycin alone (pg 12, clm 2). There would be no reason for one of skill in the art to go to Parthasarathy to investigate probucol derivatives, because the data in Siveski-Iliskovic did not indicate that a more soluble derivative of probucol would be more effective. Instead, it appears clear from the data presented in Siveski-Iliskovic that probucol alone *did* have *an* effect, but that this effect was selective and there was *no effect* on the cytotoxicity of the antineoplastic agent. The data presented in Siveski-Iliskovic did not suggest that enhancing the water solubility of the compound would cause it to have a different effect. Parthasarathy teaches that the benefit of the modifications described are that they increase the availability of free probucol (e.g. clm 2, lines 51-60). Therefore, a skilled practitioner would not be motivated to substitute the parent molecule with a derivative that was merely believed to be hydrolyzed directly to the parent molecule to investigate a different effect.

b) There is also no expectation that substituting the parent molecule with a mono- or di-ester would prove effective for enhancing cytotoxicity of an agent.

Siveski-Iliskovic teaches that the parent compound *does not* have the required utility. There is no suggestion that any modification of that compound would have any other effect. There is no suggestion in Parthasarathy that the modifications disclosed provide any additional benefit beyond water solubility and Parthasarathy is specifically directed towards methods that would increase the availability of the parent molecule. Neither of these references suggests that any amount of a probucol derivative could enhance cytotoxicity of an antineoplastic agent.

c) The references cited by the Examiner also do not teach each and every aspect of the claim.

Siveski-Iliskovic teaches that the antioxidant probucol in fact *does not* enhance cytotoxicity of an antineoplastic agent. Parthasarathy also fails to teach that any compound disclosed in that reference could be used to enhance cytotoxicity of any antineoplastic agent. Therefore, neither of the references provide any teaching of a method of administering an *effective cytotoxicity increasing amount of* a mono- or di-ester of probucol, as required by the pending claims.

The Examiner also in part relies on the assertion that it would have been inherent that a compound described in Parthasarathy would enhance cytotoxicity when administered in the amounts provided in Siveski-Iliskovic. As described above, neither of the references provide a motivation to combine the teachings, provide any expectation of success, or teach the full scope of the claims. As there is no motivation to substitute the compound described in Siveski-Iliskovic with any other compound, it cannot be inherent that in Siveski-Iliskovic that a different compound, which is neither disclosed nor suggested, would have affected cytotoxicity of adriamycin.

There is no suggestion in Siveski-Iliskovic to use a modified probucol derivative as described in Parthasarathy, there is no expectation that there would be any success using such a compound in a method of increasing cytotoxicity of an antineoplastic agent, and there is no teaching in *either* reference that a mono- or di-ester of probucol in *any* amount would be effective in enhancing the cytotoxicity of an antineoplastic agent. The combination of these references therefore does not render the pending claims obvious.

The Examiner has also rejected claims 1, 18, 23, 26, 31 and 35 under 35 U.S.C. § 103(a) over Siveski-Iliskovic and Parthasarathy further in view of Borch et al. (U.S. Patent No. 5,035,878). The Examiner relies on Borch for the assertion that it would have been obvious to

modify the combined teachings of Siveski-Iliskovic and Parthasarathy and substitute the antineoplastic agent described in Siveski-Iliskovic with another. Borch is directed to dithiocarbamic compounds of the formula [$R^1R^2NC(=S)SM$], for use in treating the toxic side effects of antineoplastic drugs such as DNA-synthesis inhibitors or alkylating 2-chloroethyl-containing drugs in mammals. No mention or suggestion of the use of esters of probucol are made in Borch.

None of the art cited by the Examiner suggests the use of mono- or di-esters of probucol to enhance the cancer cell cytotoxicity of an antineoplastic drug, or suggests combining their teachings. Similarly, none of the cited art suggests that the combination of mono- or di-esters of probucol with an antineoplastic drug would result in enhanced cytotoxicity of the drug. Borch does not remedy the deficiencies of the combination of Siveski-Iliskovic with Parthasarathy as there is no additional motivation in Borch to use an ester of probucol to enhance cytotoxicity of any antineoplastic agent.

Although Applicants believe no further fees are due with this submission, the Commissioner is hereby authorized to charge any deficiencies to Deposit Account No. 11-0980.

Respectfully submitted,

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